Nicorandil ulcer: moves beyond the mucosa

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ABSTRACT

The management of wounds is a specialty in its infancy. Success requires more than the use of dressings. All wounds require a diagnosis, a point well illustrated by the management of these cases which depended solely on stopping nicorandil.

KEYWORDS

Nicorandil – Ulcer – Wound healing

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That nicorandil (2-[(pyridine-3-ylcarbonyl)amino]ethyl nitrate), a commonly prescribed medication for angina, can cause painful ulceration is now clear. At first, nicorandil was linked with aphthous ulcers, now known to occur in 5% of patients on nicorandil.^{1–3} More recently, nicorandil has been associated with painful peri-anal,⁴ vulval⁵ and peristomal⁶ ulceration. Three further on-line reports in the *Annals* add to the body of evidence linking nicorandil with mucosal ulceration, and further extend the clinical observations. McDaid *et al.*⁷ retrospectively reviewed 44 cases of diverticular disease complicated by fistulae and showed a greater prevalence of nicorandil usage (7 of 44) compared to controls (2 of 84; $P < 0.01$). Mosley *et al.*⁸ describe a patient who almost died from haemorrhage as a consequence of progressive peri-anal mucosal ulceration induced by nicorandil. Riddell *et al.*⁹ show for the first time that nicorandil can also prevent the healing of surgical wounds, one case involving otherwise normal non-mucosal tissue. While these reports are of interest, the potential for nicorandil to prevent wound healing is noteworthy, as this extends the association beyond the mucosae.

Nicorandil, introduced in 1994, is an organic nitrate that activates soluble guanylate cyclase by binding the haem moiety, thus increasing intracellular cGMP levels to cause dephosphorylation of myosin light chain, smooth muscle relaxation and so vasodilatation. In contrast to other nitrates, as well as the vasodilating properties of calcium channel antagonists, nicorandil also causes vasodilatation by opening membrane-bound ATP-dependent potassium channels, including those within the mitochondria. The dual action reduces pre-load, after-load and also increases coronary artery blood flow; nicorandil treatment for angina was shown to reduce ischaemic heart disease end-points in

a large multicentre study.¹⁰ Nicorandil-mediated mitochondrial potassium channel opening also appears to provide a cardiac protection against ischaemic damage.¹¹ So how does nicorandil cause ulceration of mucosal membranes and surgical wounds?

It remains unclear what differentiates those patients who do and do not develop ulceration. Both sexes appear to be equally affected and ulceration can develop as early as weeks or as late as 23 months after therapy is initiated. However, ulceration seems dose dependent, as most affected patients were on higher dose (greater than 20 mg twice daily) and, in many instances, ulceration only developed after an increase in dose. The ulcers are characteristically painful, localised and extend into deeper tissue; peri-anal ulcers typically extend to the anal sphincter. Ulcers tend to have an over-hanging wound edge, with scant evidence of granulation at the base. Histological examination reveals myxoid granulation tissue, with fibrin deposition and mixed inflammatory cell infiltrate. Diffuse elastophagocytosis may be a feature, but the inflammatory infiltrate is not excessive, nor is there vasculitis or granuloma formation. Characteristically, upon discontinuing the nicorandil (which may exacerbate angina), the pain associated with the ulcer rapidly disappears (within weeks) and complete healing ensues; depending on the original size of the wound, this usually takes between 2–6 months.

If, as the growing evidence suggests, nicorandil is the cause of unwanted ulceration, it is a most unlikely culprit. Early studies in rats showed that nicorandil is as effective as cimetidine at treating experimentally induced gastric ulceration.¹² Moreover, the archetypal nitrate drug glyceryl trinitrate (GTN) is used as an effective treatment for anal fissures.¹³ Two unconvincing hypotheses have been put forward: (i) a toxic

metabolite of nicorandil excreted in the gut; and (ii) a vascular steal phenomenon. However, nicorandil metabolites are mostly excreted through the kidneys and the toxic metabolite hypothesis would not explain the abdominal wounds in the case presented by Riddell *et al.*⁹ Likewise, it is hard to rationalise the steal phenomenon, since the sites are typically well vascularised, the surrounding skin looks healthy and histological support is lacking. A more likely explanation is that nicorandil, in a dose-dependent manner, dephosphorylates myosin and so hinders the actin filament contraction that is necessary for cell migration, as would be required to repair mucosal microtrauma and surgical wounds. Could it be possible that the effect on potassium channels hinders the normal compensatory mechanisms? There is evidence that nicorandil prevents neutrophil rolling, migration and activation; an effect that is protective to cardiac myocytes after ischaemia but may hinder the early inflammatory phase of wound healing.^{14,15}

Conclusions

These cases highlight the scientific and clinical complexity of wound healing. The management of wounds is a specialty in its infancy. Success requires more than the use of dressings. All wounds require a diagnosis, a point well illustrated by the management of these cases which depended solely on stopping nicorandil.

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